REMARKS

Claim 3 has been amended to delete the phrase "biologically active fragment", and claim 9 has been amended to depend from elected claim 3. No new matter is added by any of these amendments, and entry of the amendments is requested.

35 U.S.C. § 101, Rejection of Claims 3-7, 9, 11 and 48

The Examiner had rejected claims 3-7, 9, 11 and 48 under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The instant application has provided a description of an isolated DNA encoding a polypeptide and an antibody against the polypeptide. The instant application does not disclose the biological role of the polypeptide or its significance. The instant specification asserts specific utilities for the claimed invention for diagnosis, prevention, and treatment of disorders associated with fetal development, reproduction, cell proliferation and the immune response.

These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the polypeptide encoded be SEQ ID NO:4. The disclosed polypeptide is said to have a potential function based on its amino acid sequence similarity to other known proteins. After further research, specific and substantial credible utility might be found for the claimed isolated compositions.

The Examiner characterized the instant situation to be directly analogous to *Brenner v. Manson* 148 U.S.P.Q. 689 (1966) in which a novel compound which was structurally analogous to other compounds which are known to possess anti-tumor activity was alleged to be useful as an anti-tumor agent. The court held, however, such a broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101.

The instant claims are drawn to a polynucleotide encoding a polypeptide of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the polypeptide encoded by SEQ ID NO:4 of the instant application was, as of the filing date, useful as agents for the development of treatments for the recited disorders. Until some actual and specific significance can to attributed to the

protein identified in the specification as PLBP2, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

Applicants Response

Applicants disagree that neither a specific and substantial asserted utility nor a well established utility is apparent to the skilled artisan from the specification and the knowledge of the skilled artisan at the time the application was filed.

Appellants' invention is directed to polynucleotides encoding a human phospholipid-binding protein, PLBP2 (SEQ ID NO:3), and fragments and variants thereof. PLBP2 is characterized as a member of the human phospholipid-binding protein family based on homology with a homolog from the nematode, Onchocerca PE-BP D1 (GI 1143527; SEQ ID NO:6). See specification, at page 17, lines 6-14. The polynucleotide encoding PLBP2 was initially isolated from human lung tumor tissue (LUNGTUT12) and was found by Northern analysis to be predominately found in immortalized cells or cancerous tissues, in particular, lung, prostate, heart tissues; and in fetal and tumor tissues. See specification, at page 17, lines 1-2, and lines 14-17. The claimed polynucleotides and encoded protein are therefore asserted to be useful in the diagnosis and treatment of disorders associated with fetal development, reproduction and cell proliferation, including cancer. See specification, at pages 29-30 and at pages 39-42.

The rejection of claims 3-7, 9, 11 and 48 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue, identified in the patent application as a phospholipid-binding protein, abbreviated as PLBP2, is a polypeptide encoded by a gene that was isolated from human lung tumor tissue. The novel polypeptide is demonstrated in the specification to be a member of the class of phospholipid-binding proteins, whose biological functions include molecular transport and cell signaling between membranes and the cytoplasm. See specification, at page 3. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions.

The fact that the claimed polypeptide is a member of the phospholipid-binding protein family alone demonstrates utility. Each of the members of this class, regardless of their

particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed polypeptide also has patentable utility, regardless of its actual function. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention. Appellants submit with this Response three expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references. The Furness Declaration, Rockett Declaration, Bedilion Declaration, Iyer Declaration, and the ten (10) references fully establish that, prior to the October 28, 1997 filing date of the Lal '820 application, it was well-established in the art that:

expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts; in toxicology, particularly toxicology studies conducted early in drug development efforts; and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such antibodies generate a signal that is specific to the protein, that is, produce a gene-specific expression signal;

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

failure of a probe to detect changes in expression of its cognate gene (because such changes did not occur in a particular experiment) does not diminish the usefulness of the probe as a research tool, because such information is itself useful; and

failure of a probe completely to detect its cognate transcript in any particular expression analysis experiment (because the protein is not normally expressed in that sample) does not deprive the probe of usefulness to the community of users who would use it as a research tool.

Appellants file herewith:

1. the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q (hereinafter the "Rockett Declaration");

2. the Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Bedilion Declaration");

3. the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E (hereinafter the "Iyer Declaration"); and

4. Ten (10) references published before the October 28, 1997 filing date of the Lal '820 application:

   a) PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995) (Reference No. 1)

   b) PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995) (Reference No. 2)

   c) M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995) (Reference No. 3)

   d) PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995) (Reference No. 4)

   e) U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996) (Reference No. 5)

   f) R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997) (Reference No. 6)

   g) PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997) (Reference No. 7)

h) Acacia Biosciences Press Release (August 11, 1997) (Reference No. 8)

i) V. Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (September 15, 1997) (Reference No. 9)

j) J. L. DeRisi et al., Exploring the metabolic and genetic control of gene expression on a genomic scale, Science 278:680 - 686 (October 24, 1997) (Reference No. 10)

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, Rockett Declaration, the Bedilion Declaration, and the Iyer Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene and protein expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d

1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Use of the claimed polynucleotides in disease diagnosis and treatment and in drug discovery and toxicology testing are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration, Rockett Declaration, Bedilion Declaration, and Iyer Declaration accompanying this Response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The claimed polypeptide's membership in the phospholipid-binding protein family demonstrates utility

Because there is a substantial likelihood that the claimed PLBP2 is a member of the family of polypeptides known as phospholipid-binding proteins, the members of which are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:3 in the patent application and referred to as PLBP2 in that application. Appellants have demonstrated by more than reasonable probability that PLBP2 is a member of the phospholipid-binding protein family, and that the phospholipid-binding protein family of proteins includes the phosphatidylethanolamine (PE)-binding proteins, whose human homologs function in molecular transport and signaling mechanisms between membranes and the

cytoplasm. In this regard, PLBP2 is described in the specification as having significant sequence homology with a nematode PE-BP, PE-BP D1 (GI 1143527; SEQ ID NO:6). In particular, PLBP2 and Onchocerca PLBP share 30% amino acid sequence identity over the 227 amino acid residues of PLBP2. See specification, at page 17, lines 6-14 and Figure 4. It is well-known that the probability that two unrelated polypeptides share more than 30% sequence homology over 150 amino acid residues, is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (Reference No. 11). Given homology of 30% over many more than 150 amino acid residues, the probability that the claimed polypeptide is related to PE-BP D1 is, accordingly, very high.

The Examiner must accept the applicant's demonstration that the claimed polypeptide is a member of phospholipid-binding protein family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the phospholipid-binding protein family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the phospholipid-binding protein family, useful.

While the Examiner has cited literature (See Attwood (2000), Skolnick et al. (2000) and metzler et al. (1997) cited at page 3 of the Office Action) identifying some of the difficulties that may be involved in predicting protein function, none suggest that functional homology cannot be inferred by a reasonable probability in this case. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

B. The uses of PLBP2 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene and protein expression profiling. These uses are explained in detail in the accompanying Furness Declaration, Rockett Declaration, Bedilion Declaration, and Iyer Declaration, the substance of which is not rebutted by the Patent Examiner]. There is no dispute that the claimed invention is, in fact, a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application is a continuation of, and claims priority to United States patent application Serial No. 09/390,126 filed on September 3, 1999 (hereinafter "the Lal '126 application"), which in turn was a divisional application of and claimed priority to United States patent application Serial No. 09/208,718 filed on December 9, 1998 (hereinafter "the Lal '718 application"), which in turn was a divisional application of and claimed priority to United States patent application Serial No. 08/958,820 filed on October 28, 1997 (hereinafter "the Lal '820 application"), all having the identical specification.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, e.g., in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed.

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it.

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1997 would have understood that any expressed polypeptide or expressed polynucleotide is useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies or cDNA microarrays, in connection with the development of drugs and the monitoring of the activity of such drugs. (Rockett Declaration at, e.g., ¶¶ 10-18).

It is widely understood among molecular and cellular biologists that protein expression levels provide complementary profiles for any given cell and cellular state. [Rockett Declaration, ¶ 11.]

Thus, as with nucleic acid microarrays, the greater the number of proteins detectable, the greater the power of the technique; the absence or failure of a protein to change in expression levels does not diminish the usefulness of the method; and prior knowledge of the biological function of the protein is not required. As applied to protein expression profiling, these principles have been well understood since at least as early as the 1980s. [Rockett Declaration, ¶ 14.]

It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new . . . protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the . . . protein in expression profiling studies in toxicology.[1] [Rockett Declaration, ¶ 18.]

In his Declaration, Dr. Bedilion explains why a person of skill in the art in 1997 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1997 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

C. The use of polypeptides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These

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"Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

technologies include toxicology testing, e.g., as described by Furness, Rockett, and Iyer in their Declarations.

Toxicology testing is now standard practice in the pharmaceutical industry. See, e.g., John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 12):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. ((Reference No. 12), page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 13); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 14).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 15) Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5) and published PCT applications WO 95/21944 (Reference No. 1), WO 95/20681 (Reference No. 2), and WO 97/13877 (Reference No. 7), the Acacia Biosciences Press Release (Reference No. 8), and the Glaser article (Reference No. 9).

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 9, 1995, describes an expression profiling platform, the "genome reporter matrix," which is based upon the measurement of protein

expression levels. The '588 patent further describes use of nucleic acid microarrays to measure transcript expression levels, making clear that the utility of comparing multidimensional expression data sets equally applies to protein expression data and transcript expression data.

The '588 patent speaks clearly to the usefulness of such expression analyses, particularly but not exclusively protein expression profiling, in drug development and toxicology, particularly pointing out that a protein's failure to change in expression level is a useful result. Thus, with emphasis added,

> [The invention provides] methods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug. [abstract]
>
> The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism. [column 1]
>
> The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix. [column 2]
>
> Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects. [columns 2-3]
>
> Furthermore, it is not necessary to know the identity of any of the responding genes. [column 3]

[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical. [column 4]

The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters. [column 4]

A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included. [columns 6-7]

In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug. [columns 7-8]

In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the

transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile. [column 8]

The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses. [column 8]

Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli. [column 9]

The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s). [column 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (Reference No. 8), and the September 15, 1997 news report by Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (Reference No. 9), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of nucleic acid microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods

enable diagnosis of diseases based on differential expression of genes of unknown function . . . . [abstract]

The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof. [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least

about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 – 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]

Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Applicants' assignee and published August 3, 1995, has three issued U.S. counterparts:
U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns,* or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization --

and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

> [The invention provides a] method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens. [abstract]
>
> [W]e see each individual gene product as a 'pixel' of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood. [page 2]
>
> The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts. [page 6]
>
> High resolution analysis of gene expression be used directly as a diagnostic profile. . . . [page 7]
>
> The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed. [page 7]
>
> The invention . . . includes a method of comparing specimens containing gene transcripts. [page 7]
>
> The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens. [i.e., the results yield analogous data to microarrays] [page 8]
>
> Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made. [page 8]
>
> In a further embodiment, the relative abundance of the gene transcripts in one cell

type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities. [page 9]

In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . [page 9]

[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. [pages 9-10]

The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as "gene transcript image analysis" or "gene transcript frequency analysis". The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism. [page 11]

The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few. [page 12]

[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates. [page 12]

For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . . [page 12]

In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . [page 12]

In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond. [page 12]

In a further embodiment, comparative gene transcript frequency analysis is used . .

. for the selection of better pharmacologic animal models. [page 14]

In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition. [page 14]

An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined. [page 15]

> [T]his research tool provides a way to get new drugs to the public faster and more economically. [page 36]
>
> In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker. [page 38]
>
> [T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients. [page 39]

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), filed on October 11, 1996 and published on April 17, 1997 (shortly after the April 8, 1997 filing date of the parent application for the instant U.S. Serial No. 09/203,545 application), describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the WO 97/13877 publication describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

> [T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates. [Field of the invention]
>
> An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems. [page 3]
>
> Another object of the invention is to provide a rapid and reliable method for

correlating gene expression with short term and long term toxicity in test animals. [page 3]

The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity. [page 3]

As used herein, the terms "gene expression profile," and "gene expression pattern" which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand. [page 7]

The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . [page 7]

In fact, the potential benefit to the public of having the claimed expressed polypeptide, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived

> from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequence of the claimed polypeptide and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. For example, Page et al., in discussing the identification and assignment of candidate targets, states that "rapid identification and assignment of candidate targets and markers represents a huge challenge . . . [t]he process of annotation is similarly aided by the quality and richness of the sequence specific databases that are currently available, both in the public domain and in the private sector (e.g. those supplied by Incyte Pharmaceuticals)" (Page, M.J., Amess, B.,

Rohlff, C., Stubberfield, C., Parekh, R., "Proteomics: a major new technology for the drug discovery process," Drug Discov. Today 4:55-62 (1999), Reference No. 16, enclosed, see page 58, col. 2). As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase polynucleotides encoding the claimed polypeptide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra*.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polypeptide are not "specific, and/or substantial" utilities. (Office Action at page 2.) The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention] is based on the grounds that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or

why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ [10-13]), the Rockett Declaration (at, *e.g.*, ¶¶ 10-18), the Bedilion Declaration (at, *e.g.*, ¶¶ 4-7), and the Iyer Declaration (at, *e.g.*, ¶¶ 5-10), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By explicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. The uses of PLBP2 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Examiner rejected the claims at issue on the ground that the use of an invention as tool for research is not a "substantial" use. See Office Action, at page 3. Because the Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, February 2003 revision, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration, Rockett Declaration, the Bedilion Declaration, and the Iyer Declaration. The Furness Declaration, Rockett Declaration, the Bedilion Declaration, and the Iyer Declaration demonstrate that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used.

Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the

utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore

considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. Thus the Training Materials cannot be applied consistently with the law.

CONCLUSION

Appellants request that the rejections of claims 3-7, 9, 11 and 48 under 35 U.S.C. § 101 be reversed for at least the above reasons.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 3-7, 9, 11 and 48 (Enablement)

The Examiner has rejected claims 3-7, 9, 11 and 48 under 35 U.S.C. § 112, first paragraph, specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants Response

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons. Withdrawal of the rejection of claims 3-7, 9, 11 and 48 under 35 U.S.C. § 112, first paragraph, is therefore requested.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 3-7, 9, 11 and 48 (Written Description)

The Examiner has rejected claims 3-7, 9, 11 and 38 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite, in part, a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:3. A polypeptide comprising the amino acid sequence of SEQ ID NO:3 is adequately described in the specification as filed. However, the Examiner stated, a polypeptide comprising a "naturally-occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:3" is a recitation of a genus of polypeptides for which Applicant has disclosed a single species: the polypeptide of SEQ ID

NO:3. The claim recites that the polypeptide is "naturally-occurring". The specification proposes that other members of the "naturally-occurring" polypeptide genus may be identified by using hybridization probes to identify DNAs or RNAs related to the nucleic acid encoding SEQ ID NO:3, expressing the polypeptide, and assaying the polypeptide for PLBP activity.

However, the Examiner stated, Applicant does not appear to hav provided a description of which polypeptide sequences are "naturally-occurring", even among those polypeptides at least 90% identical to the full length of the sequence of SEQ ID NO:3. Neither does Applicant appear to have provided a description of how the structure of the polypeptide of SEQ ID NO:3 relates to the structure of other "naturally-occurring" polypeptides which have PLBP activity, even for those polypeptides at least 90% identical to the full length of the sequence of SEQ ID NO:3. Thus, neither the common attributes of the genus nor the identifying attributes of individual species other than SEQ ID NO:3 appear to have been described.

One of skill in the art would conclude that Applicant was not in possession of the claimed genus of polypeptides comprising a "naturally-occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:3". The Examiner cited Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111) and University of California v. Eli Lilly and Co. (43 USPQ2d 1398) as case law supporting the written description according to 35 U.S.C. § 112, first paragraph.

The Examiner stated further that Applicant has [not] disclosed in their specification any biological fragments having PLBP activity, since Applicant has not disclosed even one species in the genus of the recited phrase "biological fragment", there is no written description for this term.

Applicants Response

The claim 3 has been amended to delete the recitation of the phrase "biologically active fragment". The phrase "naturally-occurring" is recited throughout the specification in a manner consistent with its well known meaning in the instant application to refer to polynucleotide or polypeptide identified from a natural source, such as a biological tissue.

With regard to the question of an adequate written description of the scope of the genus encompassed by "naturally-occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:3", the requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law, some of which has been recited by the Examiner.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., **complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics**. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (Emphasis added)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:3 and SEQ ID NO:4 are specifically disclosed in the application (see, for example, page 3, line 25, and page 5, lines 24-25, respectively). Variants of SEQ ID NO:3 are described, for example, at page 15, lines 23-30. In particular, the preferred, more preferred, and most preferred variants of PLBP (80%, 90%, and 95% amino acid sequence similarity to PLBP) are described, for example, at page 17, lines18-22. Incyte clones in which the nucleic acids encoding the human PLBP2 were first identified and libraries from which those clones were isolated are described, for example, at page 16, line 30 through page17, line 5 of the Specification. Chemical and structural features of PLBP2 are described, for example, on page 17, lines 6-14. Given SEQ ID NO:3, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:3 having 90% sequence identity to SEQ ID NO:3. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:3.

The Office Action has further asserted that the claims are not supported by an adequate written description because

> Applicant [does not] appear to have provided a description of how the structure of the polypeptide of SEQ ID NO:3 relates to the structure of other "naturally-occurring" polypeptides which have PLBP activity, even for those polypeptides at least 90% identical to the full length of the sequence of SEQ ID NO:3
>
> (page 4 of the Office Action)

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and antibodies which specifically bind to the proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides or polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 2 recites chemical structure to define the claimed genus:

> 2. An isolated polynucleotide sequence encoding a polypeptide selected from the group consisting of:...b) a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:3...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides or polypeptides. The polynucleotides or polypeptides defined in the claims of the present application recite structural features, and cases

such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; supra). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to phospholipid-binding proteins related to the amino acid sequence of SEQ ID NO:3. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as phospholipid-binding proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:3. The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:3" (note that SEQ ID NO:3 has 227 amino acid residues). This variation is far less than that of all potential phospholipid-binding proteins related to SEQ ID NO:3, i.e., those phospholipid-binding proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:3.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the

benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of October 28, 1997. Much has happened in the development of recombinant DNA technology in the 17 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:3 and SEQ ID NO:4, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3or SEQ ID NO:4. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides or polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

Withdrawal of the rejection of claims 3-7, 9, 11 and 48 under 35 U.S.C. § 112, first paragraph for lack of adequate written description is therefore requested.

<u>35 U.S.C. § 112, Second Paragraph, Rejection of Claim 9</u>

The Examiner has rejected claim 9 under 35 U.S.C. § 112, second paragraph, specifically because it depends from a non-elected claim.

Applicants Response

Claim 9 has been amended to depend from elected claim 6. Withdrawal of the rejection of claim 9 under 35 U.S.C. § 112, second paragraph is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited. Applicants further request that, upon allowance of claims 5 and 11, claims 13-15 and 27-28 be rejoined and examined as process claims that depend from and are of the same scope as the product claims in accordance with *In re Ochiai* and the MPEP § 821.04.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Please charge Deposit Account No. **09-0108** in the amount of **$420.00** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. 09-0108.

Respectfully submitted,
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Attachment(s):
Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with attached Exhibits A-Q
Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E
Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132

Sixteen (16) references:
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2. PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995)
3. M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995)
4. PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995)
5. U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996)
6. R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997)
7. PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997)
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15. Email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding
16. M. J. Page et al., Proteomics: a major new technology for the drug discovery process, Drug Discov. Today 4:55-62 (1999)